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COVID-19 vaccination and glomerulonephritis

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Abstract

Background: mRNA COVID-19 vaccine is more effective than traditional vaccines due to superior immune activation. However, the impact of mRNA COVID-19 vaccine on triggering de novo/relapsing glomerulonephritis (GN) is limited. We report a case series of patients who developed new or relapsing GN post vaccination.

Method: We evaluated baseline characteristics, vaccine type and clinical outcomes of 13 patients from our institution who had a new diagnosis or relapse of their GN post mRNA COVID-19 vaccination.

Results: Of 13 patients, 8 patients were newly diagnosed GNs and 5 patients had relapse. Median age was 62 years (range 19-83 years). Autoimmune disease (38%) was the most prevalent underlying disease followed by cancer (23%). Majority of patients were white male. IgA nephropathy (IgAN) was the most common GN in our series (5 patients, 38%) followed by membranous nephropathy (MN) (3 patients, 23%). One patient with IgAN had evidence of IgA deposits prior to vaccination suggesting that the immune activation following vaccination triggered a flare of the disease. Our case series also included the first case report of tip-variant focal segmental glomerulosclerosis, NELL-1 associated MN, and atypical anti-GBM nephritis. Seventy seven percent developed acute kidney injury with the majority being KDIGO stage 1 (67%). Outcome are favorable with 80% responding to therapy.

Conclusions: New cases and relapse of GN can present shortly after mRNA COVID-19 vaccination. New cases of IgAN may result from unmasking of undiagnosed IgAN due to robust immune activation rather than development of new deposits.

Introduction

Rapid and mass SARS-CoV-2 vaccination has been one of the pivotal strategies to curb the COVID-19 pandemic. The use of recently developed mRNA vaccine such as BNT 162b2 (Pfizer) and mRNA 1273 (Moderna) has provided effective protection against severe COVID-19 infection.[1,2] mRNA vaccines utilize lipid nanoparticle (LNP) as a vehicle to deliver genetically modified mRNA. Once injected, the mRNA is translated into target protein resulting in robust immune response.[3] These vaccines thus far have shown excellent safety profile and the most common immediate and short-term side effect for both mRNA vaccines has mostly involved injection site reaction. Severe reactions have been rare.[1,2] Since mass scale vaccination, however, several immune-mediated reactions including cases of myocarditis, and newly diagnosed or relapsed glomerulonephritis (GN) have been reported.[4,5] Most cases have been associated with mRNA vaccines (Pfizer and Moderna) and adenovirus vector deliveries.[6-14] However, rare cases of GN related to inactivated virus vaccine (CoronaVac from Sinovac) have also been reported.[15] The most common reported GN thus far is IgA nephropathy (IgAN). But whether COVID-19 vaccine results in an immune response that triggers IgA antibody production and formation of new deposits in the kidneys or whether the immune response to the vaccine only unmasks the presence of previously formed deposits is unclear. In this case series we report 13 cases of newly diagnosed or flares of GN post COVID-19 mRNA vaccines and provide a literature review of all the reported GN cases thus far. We also provide evidence in one case of "new" IgA nephropathy (IgAN) that the deposits were present previously. We also report on three new diagnoses following COVID-19 vaccination including a case of NELL-1 associated membranous nephropathy (MN), a case of primary focal segmental glomerulosclerosis (FSGS) and one case of atypical anti-GBM nephritis.

Method

Patient selection

Patients who were either newly diagnosed or had a relapse of their GN following vaccination are reported in this case series. All patients had their kidney pathology reviewed at Mayo Clinic, Rochester, Minnesota. Clinical data and baseline characteristics, vaccine type, onset of symptoms, laboratories on presentation, treatments and outcomes are based on review of medical records.

Literature review

We searched all literature since the inception that reported newly diagnosed or relapse of GN after any type of COVID-19 vaccines via PUBMED. We then extracted baseline characteristics, laboratories upon presentation, treatments, and outcomes.

Statistical analysis

We report continuous data with median and range. Categorical data is demonstrated with number and percentage. We used descriptive statistics in this report as the sample size is quite small and no analytical statistics were implemented.

Results

Baseline demographic and clinical characteristics of newly diagnosed and relapsed GNs

There were 13 patients reported in this case series. Of these, 8/13 (62%) cases were newly diagnosed with glomerulonephritis whereas 5/13 (38%) cases were relapses. The median age was 62 (19-83) years. Majority of patients were white (12/13, 92%) and male (9/13, 69%). Autoimmune disease (38%) was the most common comorbidity in our series followed by cancer (23%). The autoimmune diseases included DM type 1, Chron's disease, ulcerative colitis, primary sclerosing cholangitis and psoriatic arthritis. IgAN was the most common GN in our case series (5/13, 38%). The second most common GNs were MN (3/13, 23%), and primary podocytopathy (2 cases of minimal change disease, and 1 case of primary

FSGS) (3/13, 23%). Fifty four percent of our patients received mRNA-1273 (Moderna) and the other 46% received BNT 162b2 (Pfizer) vaccine. Majority of patients presented after the second dose (10/13, 77%). The median time of onset varied. Median time of onset in newly diagnosed GNs was 1 week after the 1st dose and 4 weeks after the 2nd dose. On the other hand, all of our relapse cases occurred after the 2nd dose with median onset of 3 weeks. Acute kidney injury (AKI), edema, and macroscopic hematuria were common presentations. Median serum creatinine was 1.6 (0.6- 2.5) mg/dl. Baseline clinical characteristics of each patient are demonstrated in **Table 1**.

Clinical characteristics of patients with newly diagnosed GNs

Of newly diagnosed cases (8 patients), there were four cases of IgAN, one case of MCD, one case of NELL-1 associated MN, one case of MPO-ANCA crescentic GN, and one case of atypical anti-GBM nephritis. Clinical characteristics of these patients are shown in **Table 1**. Five patients presented after the 2nd dose of the vaccine (range 2-6 weeks) and three patients presented after the 1st dose (range 1-2 weeks). The main presenting symptom in patients with new diagnosis of IgAN included AKI and gross hematuria. One patient also had a symptom of pericarditis in addition to gross hematuria at the time of presentation. One patient had history of inflammatory bowel disease which raised possibility that he may have had IgA deposits in the kidney prior to undergoing vaccination and likely had asymptomatic IgAN. This patient also had history of renal cell carcinoma and had undergone partial nephrectomy 7 years prior to his vaccination. His serum creatinine and urine studies had been normal at the time and in follow up (last value from one year prior to vaccination). In order to evaluate for presence of IgA deposits prior to vaccination, the nephrectomy sample was retrieved for further evaluation. Glomeruli were unremarkable on light microscopy. Immunofluorescence (IF) on pronase-digested, paraffin tissue was performed and showed segmental mesangial staining of IgA, kappa and lambda. Electron microscopy revealed presence of mesangial deposits. Therefore, the partial nephrectomy sample showed evidence of subclinical IgAN. We had 1 case of atypical anti glomerular basement membrane (GBM) nephritis, characterized by bright diffuse linear GBM staining for IgG, kappa and lambda on IF and mesangial proliferation and basement membrane duplication on light microscopy, without the necrotizing and crescentic phenotype typically seen in classic anti-GBM nephritis.[16]

Clinical characteristics of patients with relapse of GN

Of the 5 patients who had a relapse, two patients had underlying PLA2R-associated MN, one patient had relapse of MCD and one patient originally had diagnosis of MCD but underwent a repeat kidney biopsy upon relapse which showed tip-variant lesion of primary FSGS, and one patient had underlying IgAN. All cases of relapse occurred after the 2nd dose with onset ranging from 1-4 weeks. Clinical characteristics detail of each patient is shown in **Table 1**.

One patient with PLA2R-associated MN was in complete remission (CR) with negative PLA2R antibody titers and on no immunosuppression for 18 months prior to relapse. Upon relapse patient developed sudden onset nephrotic syndrome and PLA2R Ab was elevated at 28 IU/ml. Another patient with PLA2R-associated MN who was in remission for 8 months presented with nephrotic syndrome and PLA2R antibody titers were positive at 3 IU/ml on ELISA and positive by indirect immunofluorescence (they were both previously negative). The patient with primary FSGS was in CR and off immunosuppression for 24 months prior to relapse and presented with nephrotic syndrome. The patient with MCD was originally diagnosed with MCD 3 months prior to vaccination. She went into complete remission within 4 weeks of starting therapy with high dose steroids with proteinuria down to 200 mg/24 hours. As a result, prednisone was tapered to 5mg mg daily at which point she received her first dose of the vaccine. Three weeks after her second dose, she presented with worsening edema and was noted to have 19 grams of protein over 24 hours. The patient with IgAN on last evaluation (2 months prior to vaccination)

had serum creatinine of 0.96 mg/dL and UA showed 50-100 RBC/HPF with 431 mg of protein/ 24 hours. The patient developed gross hematuria 24 hours after the second dose of COVID-19 vaccination. He had a similar reaction following influenza vaccination a year prior.

Treatment and clinical follow-up

Nine out of 13 patients (69%) received immunosuppression [5/8 (63%) had new diagnosis and 4/5 (80%) were recurrence]. The other four patients were treated conservatively. Ten patients have available follow-up data ranging from 1-5 months. Of these, 8 patients responded to the treatments (6 treated with immunosuppression and 2 treated conservatively with angiotensin converting enzyme inhibitor (ACE-I)). Patient No. 3 who responded to therapy had developed symptoms after the first dose and had further elevation in the creatinine after the second dose (Peak creatinine 2.2 mg/dL) which then subsequently improved to 1.4 mg/dL. One patient with IgAN and AIN and the patient with atypical anti-GBM nephritis were both treated with immunosuppressive therapy but have not yet responded and have had progression of their kidney disease. Both of these patients developed symptoms after the first dose of the vaccine but proceeded to receive the second dose. Additional treatment details and outcomes are outlined in **Table 2**.

Clinical characteristics of patients from published literatures

We found a total of 20 articles related to COVID-19 vaccines and glomerulonephritis published since inception until July 25th, 2021. There were 27 cases including 13 cases of newly diagnosed GNs (48%) and 14 cases of relapse (52%) (**Table 3**). IgAN was the most common pathology (11 cases (41%): 4 new and 7 relapse) followed by MCD (10 cases (37%): 4 new and 6 relapse). Other pathologies including 2 cases of anti-GBM (7%) (both new cases), 2 case of ANCA vasculitis (7%) (both new cases, 1 case of MPO-ANCA and 1 case of PR3 ANCA), 1 case of ANCA-negative granulomatous vasculitis (4%) (relapse), and 1 case of PLA2R-associated MN (4%) (relapse). Median age was 41 years and 48% were male. However, patients tended to be younger in the relapse group (median age 38 years) compared to newly diagnosed group (median age 56 years) (**Table 4**).

BNT 162b2 (Pfizer) vaccine was the most common vaccine administered (15/27 patients, 55%) followed by mRNA-1273 (Moderna) (8/27 patients, 30%). There were 3 patients receiving Astrazeneca vaccine (11%) and only a single patient receiving inactivated vaccine (4%) (CoronaVac by Sinovac) (**Table 4**).

Of 27 patients, 15 patients (56%) developed symptoms after the 1st dose whereas the remaining (12 patients, 44%) developed after the 2nd dose. However, newly diagnosed GN patients tended to develop after second dose (7/13 patients, 54%) and relapses tended to develop after first dose (9/14 patients, 64%) (**Table 4**).

Clinical characteristics and follow-up of patients by disease

IgA nephropathy

In our case series, there were 5 cases of IgAN (4 new and 1 relapse). In the literatures, there were 11 cases of IgAN reported (4 new and 7 relapse). Gross hematuria was the most common presentation followed by acute kidney injury. However, in majority of patients the gross hematuria was often self-limited and seldom required immunosuppression. Of the total of 16 patients, only 3 patients received immunosuppression and one patient had super-imposed AIN as well. All cases of relapsed IgA improved spontaneously within 1-2 weeks.

Primary podocytopathy
In our case series, there were 2 cases of MCD (1 new and 1 relapse) and one case that was previously MCD but on repeat biopsy showed a tip-variant FSGS lesion. In the literatures, there were 10 cases (4 new and 6 relapse). All cases in our series developed symptoms after the 2nd dose whereas all MCD cases in the literature developed symptoms after the 1st dose. All patients received immunosuppression. One patient with new MCD responded rapidly to therapy. One patient with relapse of MCD did not respond to high-dose steroids and received rituximab to which the patient responded. The patient with primary FSGS had partial response to prednisone in combination with tacrolimus.

Membranous nephropathy
In our case series, there were 3 cases of MN in which two cases were associated with PLA2R (relapse) and 1 case with NELL-1 (new). The NELL-1 associated MN patient had age-appropriate cancer screening completed which were negative. Based on the literature review, there has been one case of PLA2R-associated MN after inactivated vaccine. All patients in our series developed nephrotic syndrome after the 2nd dose. The patient with NELL-1 associated MN significantly improved after conservative management. Proteinuria improved from 6.5 g/d to 0.4 g/d within three months after angiotensin converting enzyme inhibitor initiation. Of two patients with PLA2R-asociated MN, only one patient from our series has follow-up data. The patient was restarted on tacrolimus. At 1 month, proteinuria and serum albumin improved from 8.7 g/d to 5.7 g/d and 2.0 g/dl to 2.9 g/dl respectively.

Anti-GBM and ANCA-associated vasculitis
In our case series, there was one case of atypical anti-GBM nephritis. In the literatures, there have been two cases of classic anti-GBM nephritis. The patient from our series presented one week after the 1st dose with symptom of uncontrolled hypertension (sBP> 200 mmHg) whereas the other two cases from literatures presented within two weeks after the 2nd dose. Outcome data was available in two patients (one from our series and another from the literature). Our patient did not respond to mycophenolate and high dose steroid and serum creatinine continued to rise. He has now been initiated on cyclophosphamide but too early to know the response. Another patient received cyclophosphamide, plasmapheresis and high dose steroid but patient did not respond and has remained on dialysis.

We had one patient with MPO-ANCA associated vasculitis (AAV) and in the literature, there were two cases of ANCA-associated vasculitis, one associated with MPO and another with PR3. In addition, there was a single case report of ANCA-negative granulomatous vasculitis post adenoviral vector vaccine. Our patient presented with shortness of breath and fatigue 4 weeks after the 2nd dose. The patient was found to have AKI, serum creatinine of 2.5, with microscopic hematuria and subnephrotic range proteinuria. Subsequently, serum creatinine increased to 3.1 and a kidney biopsy was done which revealed pauci-immune crescentic GN. The patient was treated with rituximab and high dose prednisone and serum creatinine one-month post treatment improved at 2.3 mg/dl. From the literature, the MPO-ANCA and ANCA-negative granulomatous vasculitis patients responded to therapy with improvement in serum creatinine. In contrast, the patient with PR3-AAV required initiation of dialysis.

Discussion
Our case series is the largest series to report on both newly diagnosed and relapsed cases of GN post COVID-19 vaccination. All patients in our series received mRNA vaccines. The BNT162b (Pfizer) and mRNA-1273 (Moderna) are the two most widely used vaccines in the United States after their use was approved under emergency use authorization by the FDA. Most patients in our series developed kidney-related symptoms after the second dose, but the onset of symptoms varied from one week after the first dose to six weeks after the second dose. Taking into account cases reported in the literature, the

onset of symptoms have been reported as early as few hours after the first dose.[17-19] It is possible that some patients in our series may have had signs of kidney injury (e.g. elevated creatinine, proteinuria or microscopic hematuria) between the first and second dose but had not been medically evaluated in that interim. In addition, the three patients who had developed symptoms after the first dose, proceeded to receive the second dose as their presentations at the time were not attributed to the COVID-19 vaccine. Even though the median age was 62 years, the range varied from 19 to 83 years of age. This wide range of presentations has also been noted in the other recent reports in the literature ranging from 13 to 80 years of age (**Table 4**).

mRNA vaccine has been developed and refined for nearly two decades but was not used clinically until only recently.[20] The vaccine contains purified modified mRNA and a vehicle which helps deliver mRNA into host cells.[20] After injection, mRNA will be translated into target protein which in turn results in immune system activation. Growing evidence from several large phase 3 randomized controlled trials and real word data have shown superiority of mRNA vaccine over inactivated vaccine.[1,2,21,22] This may be partly due to their ability to induce robust cell-mediated and antibody mediated immune responses.[3] Indeed they have been shown to induce neutralizing antibody to the level far beyond convalescent serum.[23] Moreover, the neutralizing antibody after mRNA vaccine appear to be higher than that of adenoviral vector COVID-19 vaccine.[23] The cell-mediated response results from upregulation of CD4+ and CD8+ T cells accompanied by increasing interferon γ secretion.[3] The CD4+ T cell response from mRNA vaccine has been shown to confer partial protection to non-ancestral strain of SARS-CoV-2 and endemic corona virus suggesting immune crossover.[24] Similarly, another study has shown cross-reactivity of antibody to SARS-CoV-2 spike protein and nucleocapsid to other self-human antigens such as transglutaminase 3, extractable nuclear antigen, myelin basic protein, mitochondria, α-myosin, thyroid peroxidase, collagen, and claudin.[25] Therefore, it is conceivable that this higher immunogenicity and cross reactivity could lead to unexpected and perhaps non-specific immune activation that may aggravate, unmask or incite autoimmune processes. Similar to the cases of glomerulonephritis, this immune activation following mRNA COVID-19 vaccination has been associated with cases of myocarditis particularly in young male.[5] A detailed investigation in a single patient with myocarditis demonstrated upregulated specific NK cells but absence of Th17 and certain cytokines that are commonly associated with myocarditis suggesting that underlying host related factors can play a role in development of autoimmunity.[4] Indeed, we observed a high prevalence of autoimmune diseases in our series and it is likely this underlying immune dysregulation is a risk factor for development of glomerulonephritis or relapse of the disease.

It is noteworthy that many of the reported GNs in association with COVID-19 vaccination have also been noted with the COVID-19 infection itself. Podocytopathy and collapsing glomerulopathy in addition to cases of anti-GBM disease and ANCA associated vasculitis have all been reported.[26-29] The pathophysiology of GNs in association with COVID-19 infection is complex and may include direct cytotoxicity to the podocytes in addition to immune dysregulation.[27,28] It is possible that the immune response to COVID-19 vaccine mimics what happens in response to natural infection thus resulting in glomerulonephritis in susceptible patients.

Relapse of glomerulonephritis following vaccination when there is upregulation of both cell-mediated (e.g. in cases of relapse of MCD)[30] and antibody-mediated immunity (e.g. relapse of PLA2R-associated MN) is conceivable. But why do some patients develop new glomerulonephritis? One possibility is that they have underlying immune dysregulation which in turn makes them pre-disposed to development of glomerulonephritis. As noted above, 38% of the individuals in our series had altered autoimmunity at baseline. Another possibility is that the disease perhaps was present prior to the vaccination, but patient

was clinically asymptomatic. This may be the case in patients with new IgAN. We were able to show for the first time that in at least one patient with "new" diagnosis of IgAN that the IgA deposits were indeed present prior to the vaccination. This patient had a prior partial nephrectomy sample available from 7 years prior and review of this sample confirmed IgA deposits. This case provides proof that in some individuals the vaccine only results in a "flare" of the already present disease rather than development of new IgA antibodies that are deposited in the kidney. Although, we cannot confirm this finding in other cases of IgAN due to lack of pre-vaccination kidney specimen, it is likely that cases with earlier onset of symptoms post vaccination have already had IgA deposits. IgAN was the most commonly noted GN post COVID-19 vaccination both in our series and based on review of the literature. This finding might be explained by the fact that IgA comprises the major antibody response early following mRNA COVID-19 vaccination.[31]

The development of glomerulonephritis (e.g. IgAN and MCD) following vaccination is not new and has been reported in humans and animal models.[32-34] It is likely that the mRNA vaccine results in a more potent immune response and therefore associated with a higher rate of GN compared to other types of vaccine (inactivated virus). It is important to also note that this unwanted immune activation occurs in only a very small percentage of vaccinated patients. The exact incidence is unknown as some cases may not have been reported in the literature or may not have been recognized. The rarity of GNs post COVID-19 vaccine may be similar to the cases of myocarditis in association with the mRNA vaccines and thus far, CDC endorses continuation of COVID-19 vaccination due to benefit over risk profile.[5]

At this point in time outcome of newly diagnosed and relapsed GNs post COVID-19 vaccine appears favorable in patients with nephrotic syndrome and IgAN. Most IgAN cases who presented with gross hematuria spontaneously remitted without specific intervention. About 69% of patients in our case series developed AKI but majority of them developed AKI stage 1. Of the 10 patients with available follow-up data, eight have responded to therapy (conservative and immunosuppression). One case of IgAN has had a progressive course. This patient however, also had features of AIN on his kidney biopsy which may have contributed to progression of the disease. On the other hand, patients with anti-GBM and ANCA-associated vasculitis particularly appear to have fewer desirable outcomes. One patient with atypical anti-GBM nephritis has had progressive disease following treatment with high dose steroids and mycophenolate mofetil. His treatment has been changed to cyclophosphamide and additional follow-up at this point is not available. None of the patient from our case series required dialysis. However, there were 2 patients from the literature including anti-GBM and PR3-ANCA vasculitis, that did not respond to therapy, and thus required dialysis initiation. Taken together, out of 40 reported cases, only two patients (5%) have been reported to require dialysis. Longer term follow-up is needed to better understand the trajectory and kidney outcome of these patients.

Our case series has limitations. Even though it is the largest series reported thus far the sample size is still limited. This is likely in part due to the fact that the incidence is low, but we cannot exclude the possibility that some cases may have been missed. Another limitation is lack of long-term data on these patients. Even though in short-term outcomes seem favorable we need longer term follow up of these patients. Finally, we cannot prove with certainty that the vaccine resulted in development of new or relapse of the GN but certainly the temporal association is compelling.

In summary, this case series in combination with cases published thus far in the literature provides data on 40 patients with new and relapsed GN post mRNA COVID-19 vaccine. As mass vaccination efforts continue, and the overwhelming benefits of vaccination for individuals with chronic kidney disease who are at increased risk of devastating COVID-19 complications (including death, dialysis, long COVID),

nephrologists and other physicians should be aware of this association and remain vigilant when evaluating patients post vaccination especially when there are symptoms of kidney-related injury present.

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Table 1: Characteristics of initial presentation of newly diagnosed and relapsed glomerulonephritis patients post COVID-19 vaccination

Case	Age	Sex	Race	Diagnosis	Vaccine	Onset after which dose	Onset time (weeks)	Presenting symptoms	Baseline SCr (mg/dl)	Laboratories during presentation			
										SCr (g/dl)	Urine RBC (/HPF)	Urine protein (g/d)	SAlb (g/dl)
New cases													
1	38	M	W	IgAN	Pfizer	2nd	2	Gross hematuria	1.3	1.6	51 – 100	0.32	NA
2	44	M	W	IgAN + acute interstitial nephritis	Moderna	1st	2	AKI	1.1	2.5	21 – 30	14	3.7
3	66	M	W	IgAN	Moderna	1st	2	Gross Hematuria	1.1	1.5*	51 – 100	1.2	4.1
4	62	M	W	IgAN	Pfizer	2nd	6	AKI	1	2.2	31 – 40	0.9	4.2
5	77	M	W	Atypical anti-GBM nephritis	Pfizer	1st	1	Hypertension	1	1.8	51 – 100	1.6	NA
6	83	M	W	MCD + ATN	Moderna	2nd	4	AKI	1.19	2.19	<3	18	2.0
7	50	F	W	NELL-1 MN	Pfizer	2nd	4	Joint pain and proteinuria	0.84	0.7	3 – 10	6.5	3.5
8	82	F	W	MPO-ANCA	Moderna	2nd	4	AKI, hematuria, proteinuria	0.8	2.5**	3 – 10	1.2	NA
Relapsed cases													
9	67	F	W	MCD	Moderna	2nd	3	Edema	1	1.6	<3	19	2.5
10	29	F	A	FSGS (tip variant)	Pfizer	2nd	3	Edema	0.6	0.6	<3	10	2.2
11	39	M	W	PLA2R MN	Pfizer	2nd	1	Edema	0.91	1.13	3 – 10	8.7	2
12	70	M	W	PLA2R MN	Moderna	2nd	4	Edema	1.7	2.1	<3	16.6	2.7
13	19	M	W	IgAN	Moderna	2nd	1	Gross Hematuria	0.96	0.76	11 – 20	0.61	4.5

Abbreviations: M: male, F: female, W: White, A: Asian, IgAN: IgA nephropathy, MCD: minimal change disease, FSGS: focal segmental glomerulosclerosis, ATN: acute tubular necrosis, MN: membranous nephropathy, MPO-ANCA: myeloperoxidase-antineutrophilic cytoplasmic antibody, PLA2R: phospholipase A2 receptor, GBM: glomerular basement membrane, R: response, NA: Non-available, F/U: follow-up, SCr: serum creatinine, RBC: red blood cell, HPF: high power field, SAlb: serum albumin

* Serum creatinine peaked at 2.2 mg/dL.

** Serum creatinine peaked at 3.1 mg/dl.

Table 2: Treatment and follow-up of patients with newly diagnosed and relapsed glomerulonephritis post COVID-19 vaccination

Case	Age	Sex	Diagnosis	Vaccine	Treatment	Response	F/U time (months)	Laboratories during last follow-up				Duration of remission before relapse (m)
								SCr (g/dl)	Urine RBC (/HPF)	Urine protein (g/d)	SAlb (g/dl)	
New Cases												
1	38	M	IgAN	Pfizer	Conservative	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	NA
2	44	M	IgAN+ interstitial nephritis	Moderna	High dose steroid	NR	3	3.6	3 – 10	5.6	3.8	NA
3	66	M	IgAN	Moderna	Prednisone*	R	5	1.4	3 – 10	0.3	NA	NA
4	62	M	IgAN	Pfizer	Conservative	R	1.5	2.0	<3	0.2	NA	NA
5	77	M	Atypical anti-GBM	Pfizer	Prednisone + Mycophenolate	NR	1.5	2.9	51 – 100	0.3	4	NA
6	83	M	MCD+ATN	Moderna	High dose steroid	R	1	1.2	<3	2	2.7	NA
7	50	F	NELL-1 MN	Pfizer	Conservative	R	2	0.7	<3	0.4	4.3	NA
8	82	F	MPO-ANCA	Moderna	High dose steroid+ Rituximab	R	1	2.3	NA	NA	NA	NA
Relapsed Cases												
9	67	F	MCD	Moderna	High dose steroid + Rituximab	R	2	1.5	0-2	0.07	4.4	1
10	29	F	Primary FSGS	Pfizer	High dose steroid + tacrolimus	R	3.5	0.7	<3	3.7	3.2	24
11	39	M	PLA2R MN	Pfizer	Tacrolimus	R	1	1.1	3 – 10	5.7	2.9	18
12	70	M	PLA2R MN	Moderna	Obinutuzumab	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	8
13	19	M	IgAN	Moderna	Conservative	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	6

Abbreviations: M: male, F: female, IgAN: IgA nephropathy, MCD: minimal change disease, ATN: acute tubular necrosis, FSGS: focal segmental glomerulosclerosis, MN: membranous nephropathy, PLA2R: phospholipase A2 receptor, GBM: glomerular basement membrane, R: response, NR: no response, NA: Non-applicable, F/U: follow-up, SCr: serum creatinine, RBC: red blood cell, HPF: high power field, SAlb: serum albumin
*prednisone was initiated for treatment of pericarditis

Table 3: Summary of published cases of newly diagnosed and relapsed glomerulonephritis

Authors	Case	Age	Sex	Underlying disease	Vaccine	Symptoms	Onset after which dose	Onset	Diagnosis	Treatments	Outcomes
New Cases											
Lebedev et al[10]	1	50	M	No	mRNA (Pfizer)	Nephrotic syndrome, AKI, HTN	1st	Day 10	MCD	High dose steroid	Proteinuria and AKI significantly improved at 2 weeks.
D'Agati et al[6]	2	77	M	DM type 2	mRNA (Pfizer)	Nephrotic syndrome, AKI, HTN	1st	1 week	MCD	High dose steroid	Proteinuria and SCr not improved at 3 weeks.
Holzworth et al[7]	3	63	F	HTN, tobacco dependence	mRNA (Moderna)	Nephrotic syndrome, uncontrolled HTN	1st	< 1 week	MCD	High dose steroid	NA
Maas et al[35]	4	80	F	NA	mRNA (Pfizer)	Nephrotic syndrome, HTN	1st	1 week	MCD	High dose steroid	Proteinuria reduced from 15 g/d->0.7 g/d at day 10.
Sekar et al[12]	5	52	M	HTN	mRNA (Moderna)	Headache, AKI, hematuria	2nd	2 weeks	PR3- ANCA vasculitis	RTX (side effects) then IV CyC + steroid was started	Dialysis was started. 2nd dose of IV CyC was planned.
Shakoor et al[36]	6	78	F	HTN, DM type 2	mRNA (Pfizer)	AKI, hematuria, proteinuria	1st	2 weeks	MPO-ANCA vasculitis	High dose steroid and RTX	SCr improved from 3.5 to 2.3 mg/dl.
Gillion et al[13]	7	77	M	No	Adenovirus vector (AstraZeneca)	Fever, night sweat, and AKI	1st	4 weeks	ANCA-negative granulomatous vasculitis	High dose steroid	SCr was normalized at 4 weeks.
Kudose et al[37]	8	50	F	HTN, APS	mRNA (Moderna)	Gross hematuria	2nd	Day 2	IgAN	Conservative	Hematuria resolved in 5 days.

	9	19	M	Microscopic hematuria	mRNA (Moderna)	Gross hematuria	2nd	Day 2	IgAN	Conservative	Hematuria resolved in 2 days.
Tan et al[38]	10	41	F	GDM	mRNA (Pfizer)	Gross hematuria	2nd	Day 1	IgAN	High dose steroid+ IV CyC	NA
	11	60	M	Hyperlipidemia	mRNA (Pfizer)	Gross hematuria	2nd	Day 1	Anti-GBM	High dose steroid+oral CyC+PLEX	NA
Hanna et al[17]	12	17	M	No	mRNA (Pfizer)	Gross hematuria, AKI, proteinuria	2nd	<24 h	IgAN	High dose steroid	SCr improved (duration not reported).
Sacker et al[39]	13	-	F	No	mRNA (Moderna)	AKI, hematuria, proteinuria	2nd	2 weeks	Anti-GBM	High dose steroid, CyC, PLEX	Remained dialysis dependent.
Relapsed Cases											
Negrea et al[18]	1	38	F	IgAN in remission	mRNA (Moderna)	Macroscopic hematuria	2nd	8-24 h	IgAN	Conservative	Spontaneously resolved.
	2	38	F	IgAN in remission	mRNA (Moderna)	Macroscopic hematuria	2nd	8-24 h	IgAN	Conservative	Spontaneously resolved.
Perrin et al[11]	3	22	M	IgA vasculitis	mRNA (Moderna)	Macroscopic hematuria	1st	Day 2	IgAN	Conservative	Spontaneously resolved.
	4	41	F	Kidney transplant	mRNA (Pfizer)	Macroscopic hematuria	1st	Day 2	IgAN	Conservative	Spontaneously resolved.
	5	27	F	On hemodialysis	mRNA (Pfizer)	Macroscopic hematuria	2nd	Day 2	IgAN	Conservative	Spontaneously resolved.
Hanna et al[17]	6	13	M	DM type 1	mRNA (Pfizer)	Gross hematuria, AKI	2nd	<24 h	IgAN	Conservative	Hematuria and AKI resolved within 1 week.
Rahim et al[19]	7	52	F	IgAN treated with ACEi	mRNA (Pfizer)	Gross hematuria, worsening proteinuria	2nd	<24h	IgAN	Conservative	Hematuria resolved within 1 week.
Schwotzer et al[40]	8	22	M	Steroid-dependent MCD	mRNA (Pfizer)	Nephrotic syndrome	1st	Day 3	MCD	High dose steroid+ TAC	Remission was achieved at Day 17 after treatment.

Kervella et al[8]	9	34	F	Steroid-dependent MCD	mRNA (Pfizer)	Nephrotic syndrome	1st	Day 10	MCD	High dose steroid	Remission was achieved shortly after treatment.
Komaba et al[9]	10	65	M	MCD in remission	mRNA (Pfizer)	Nephrotic syndrome	1st	Day 19	MCD	High dose steroid + cyclosporine	Remission was achieved at 2 weeks.
Morlidge et al[14]	11	30	M	MCD previously treated with RTX, TAC and prednisone	Adenovirus vector (AstraZeneca)	Foamy urine	1st	Day 2	MCD	High dose steroid	Remission was achieved at 10 days.
	12	40	F	MCD on prednisone and TAC maintenance	Adenovirus vector (AstraZeneca)	Foamy urine	1st	Day 2	MCD	High dose steroid	Remission was achieved at 2 weeks.
Mancianti et al[41]	13	39	M	MCD in remission for 37 y	mRNA (Pfizer)	Nephrotic syndrome	1st	1 week	MCD	High dose steroid	Remission was achieved at 4 weeks.
Aydin et al[15]	14	66	F	HTN; DM type 2; MN previously on cyclosporine and steroid but off 7 y ago	Inactivated virus (Sinovac)	Nephrotic syndrome, AKI	1st	2 weeks	PLA2R-associated MN	NA	NA

Abbreviations: M: male, F: female, AKI: acute kidney injury, DM: diabetes mellitus, GDM: gestational diabetes, HTN: hypertension, APS: antiphospholipid syndrome, IgAN: IgA nephropathy, MCD: minimal change disease, MN: membranous nephropathy, PLA2R: phospholipase A2 receptor, PR3: proteinase 3, MPO: myeloperoxidase, ANCA: antineutrophil cytoplasmic antibodies, GBM: glomerular basement membrane, NA: Non-applicable, SCr: serum creatinine, RTX: rituximab, CyC: cyclophosphamide, IV: intravenous, PLEX: plasma exchange, ACEi: angiotensin converting enzyme inhibitor; TAC: tacrolimus

Table 4: Clinical characteristics of GN patients post COVID-19 vaccine from previously published literatures and current case series

Characteristics	Current case series (n=13)	Literatures (n=27)	Total (n=40)
Age (years)	62 (19-83)	41 (13-80)	50 (13-83)
Male sex (%)	9 (69%)	13 (48%)	22 (55%)
Underlying disease			
- Autoimmune disease	5 (38%)	NA	NA
- Diabetes	2 (15%)	NA	NA
- Cancer	3 (23%)	NA	NA
New vs Recurrent disease			
- New	8 (62%)	13 (48%)	21 (53%)
- Recurrent	5 (38%)	14 (52%)	19 (47%)
Diagnosis			
- IgA nephropathy	5 (38%)	11 (41%)	16 (40%)
- Minimal change disease	2 (15%)	10 (37%)	12 (30%)
- Membranous nephropathy	3 (23%)	1 (4%)	4 (10%)
- Anti-GBM disease	1 (8%)	2 (7%)	3 (7%)
- ANCA vasculitis	1 (8%)	2 (7%)	3 (7%)
- Focal segmental glomerulosclerosis	1 (8%)	-	1 (3%)
- ANCA negative granulomatous vasculitis	-	1 (4%)	1 (3%)
Vaccine type			
- BNT-162b2 (Pfizer)	6 (46%)	15 (55%)	21 (53%)
- mRNA-1273 (Moderna)	7 (54%)	8 (30%)	15 (37%)
- Adenovirus vector (AstraZeneca)	-	3 (11%)	3 (7%)
- Inactivated vaccine (CoronaVac by Sinovac)	-	1 (4%)	1 (3%)
Symptoms occur after 1st or 2nd dose			
- 1st dose	3 (23%)	15 (56%)	18 (45%)
- 2nd dose	10 (77%)	12 (44%)	22 (55%)
Onset			
- New case s/p 1st dose	1 (1,2)	1 (1,4)	1 (1,4)
- New case s/p 2nd dose	4 (2,6)	1 (1,2)	2 (1,6)
- Relapse case s/p 1st dose	-	1 (1,2)	1 (1,2)
- Relapse case s/p 2nd dose	3 (1,4)	1 (1,1)	1 (1, 4)
Laboratory on presentation			
- Serum creatinine (mg/dl)	1.6 (0.6, 2.5)	1.7 (0.7, 8.4)	1.7 (0.6, 8.4)
- Serum albumin (g/dl)	3.1 (2, 4.5)	2.7 (0.7, 4.7)	2.9 (0.7, 4.7)
- Hematuria (%)	9 (75%)	15 (58%)	24 (63%)
- Urine protein (g/d)	6.5 (0.3, 19)	2.0 (0.3, 23.2)	2.2 (0.3, 23.2)
Treatment			
- Conservative management	4 (31%)	9 (33%)	13 (32%)
- Immunosuppression	9 (69%)	18 (67%)	27 (68%)

Outcome*			
- Response	8 (80%)	21 (91%)	29 (88%)
- Not response	2 (20%)	2 (9%)	4 (12%)

*There were only 10 patients in our case series and 23 patients from the literatures with follow-up outcome